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1,174,493

PATENT SPECIFICATION

NO DRAWINGS

1,174,493

Inventors: PHILIPPE ROHRBACH and JEAN BLUM

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International Classification:—C 07 d 49/38

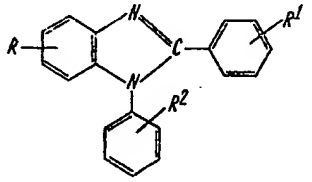
COMPLETE SPECIFICATION

New Benzimidazoles and process for their preparation

We, MANUFACTURES J. R. BOTTU, a French Body Corporate of, 117 Rue Notre Dame des Champs, Paris 6e, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to benzimidazoles and their preparation.

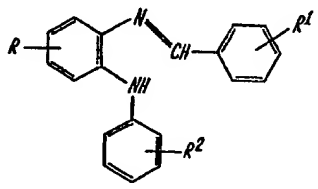
The present invention provides, as new compounds, the benzimidazoles of the formula:



I

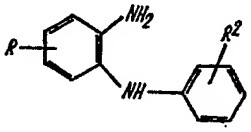
in which R represents hydrogen, halogen, trifluoromethyl, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms, and R^1 and R^2 are the same or different and are each halogen, trifluoromethyl, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, hydroxy, amino-alkoxy of 1 to 4 carbon atoms, alkylaminoalkoxy of 1 to 4 carbon atoms in each alkyl residue, dialkylaminoalkoxy of 1 to 4 carbon atoms in each alkyl residue, or carboxy, and their acid addition salts.

According to a feature of the invention, the benzimidazoles of formula I are made by the oxidation of a compound of the formula:



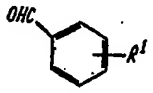
II

in which R, R^1 and R^2 are as hereinbefore defined. The intermediates of formula II are themseleves prepared by the reaction of an *N*-phenyl-*ortho*-phenylenediamine of the formula:



III

with a benzaldehyde of the formula:



IV

where R, R^1 and R^2 are as hereinbefore defined.

[*Price 4s. 6d.*]

The oxidation of the compounds of formula II is carried out by the reaction of Hinsberg and Koller (Ber. *29*. 1498, (1896)) as modified by Jerchel *et al* (*Ann. 575*, 162—73 (1952)), that is to say by heating the compound of formula II with an aromatic nitro compound such as nitrobenzene or *meta* - dinitrobenzene either in the absence of a solvent or in the presence of a suitable inert solvent such as acetic acid. The reaction temperature may be, e.g., from 50° to 300°C., and generally is most conveniently the boiling temperature of the reaction mixture provided that the latter is within the aforesaid temperature range. The time required to complete the reaction varies with the starting materials used, but a heating period of from 10 minutes to one hour is generally suitable. The desired benzimidazole of formula I may be isolated and purified by any suitable conventional method such as removal of the solvent in which the reaction takes place and recrystallisation of the residue from an appropriate solvent.

The reaction between the compounds of formulae III and IV is conveniently carried out by heating equimolar quantities of the reactants in the presence of an inorganic solvent such as an alcohol, preferably ethanol, in the presence or absence of a dehydration catalyst such as zinc chloride or titanium chloride. It is generally convenient to operate at the reflux temperature of the reaction mixture for a time generally from one half to six hours. The product is generally sufficiently pure to be used for the oxidation step without further purification, but can if desired be isolated and recrystallised in conventional manner.

The compounds of Formula III may be prepared by the known method described in Zhur. Obschchei. Khim. *23*, 1583—93 (1953) starting from appropriately substituted *ortho*-chloro-nitrobenzenes and anilines.

The acid addition salts of the benzimidazoles of formula I may be prepared in conventional manner, for example by the action of the theoretical quantity of a mineral or organic acid on a base of formula I.

The benzimidazoles of formula I and their non-toxic acid addition salts have interesting toxicological and pharmacodynamic properties, and are, in particular, useful as anti-inflammatories and analgesics of very low toxicity.

The following Examples illustrate the present invention.

Example 1

(A) 4 - Methoxyphenyl - *ortho* - phenylenediamine (10.5 g.), 4 - methoxybenzaldehyde (6.5 g) and methanol (40 ml.) are introduced into a 100 ml. round-bottom flask provided with a reflux condenser. The mixture is refluxed for one hour and then allowed to cool. A brown oil is obtained which crystallises slowly. *N* - (4 - methoxyphenyl) - *N'* - (4-methoxybenzylidene) - *ortho* - phenylenediamine (10.5 g., 63% yield) is obtained as yellow crystals, m.p. 122°C.

(B) This compound (10.5 g.) and nitrobenzene (11 ml.) are introduced into a 100 ml. round-bottom flask provided with a reflux-condenser. The mixture is heated at about the boiling point for 15 minutes and then allowed to cool. The crystals formed are separated and washed with petroleum ether. 1,2-Bis(4 - methoxyphenyl) - benzimidazole (9.4 g., 90% yield) is obtained as chamois coloured crystals, m.p. 151°C., after recrystallisation from ethanol.

Analysis: calculated for $C_{21}H_{18}N_2O_2$, N% = 8.48; found, N% = 8.3.

Example 2

Proceeding as described in Example 1(A), *N* - (4 - methoxyphenyl) - *N'* - (4 - methoxybenzylidene) - 5 - methoxy - *ortho* - phenylenediamine (12 g., 86.7% yield) is obtained as yellow crystals, m.p. 92°C. from *N* - (4-methoxyphenyl) - 5 - methoxy - *ortho* - phenylenediamine (9 g.) with 4 - methoxy - benzaldehyde (5 g.) in ethanol (35 ml.).

This compound (12 g.) is heated in nitrobenezene (15 ml.) as described in Example 1(B), and 6 - methoxy - 1,2 - bis(4 - methoxyphenyl)benzimidazole (6 g., 50% yield) is obtained as clear beige crystals, m.p. 160°C., after recrystallisation from isopropanol.

Analysis: calculated for $C_{22}H_{20}N_2O_3$, N% = 7.78; found, N% = 7.8.

Example 3

Proceeding as described in Example 1(A), *N* - (4 - methoxyphenyl) - 4 - methyl - *ortho*-phenylenediamine (24 g.) is heated with 4-methoxy - benzaldehyde (14 g.) in ethanol (100 ml.) and *N* - (4 - methoxyphenyl) - *N'*-(4 - methoxy - benzylidene) - 4 - methyl-*ortho* - phenylenediamine (32 g.) is obtained as an oil which is utilised in the next step without further purification.

The aforesaid oil (32 g.) is heated in nitrobenzene (40 ml) as described in Example 1(B), and 5 - methyl - 1,2 - bis(4 - methoxyphenyl)-benzimidazole (10 g., 32% yield) is obtained, m.p. 173°C. after recrystallisation from isopropanol.

Analysis: calculated for $C_{22}H_{20}N_2O_2$, N% = 8.13, found, N% = 8.0.

Example 4

Proceeding as in Example 1(A), *N* - (4-methoxyphenyl) - 4 - methoxy - *ortho*-phenylenediamine (21.5 g.) is heated with 4 - methoxybenzaldehyde (12 g.) in ethanol (80 ml.) and *N* - (4 - methoxyphenyl) - *N'* - (4-methoxybenzylidene) - 4 - methoxy - *ortho*-phenylenediamine (33 g.) is obtained in the form of an oil which is used without further purification in the next step.

The aforesaid oil (33 g.) is heated in nitrobenzene (41 ml.) as described in Example 1(B),

and 5 - methoxy - 1,2 - bis(4 - methoxyphenyl)benzimidazole (10 mg., 31% yield) is obtained as clear beige crystals, m.p. 140°C., after recrystallisation from isopropanol.

Analysis: Calculated for $C_{22}H_{20}N_2O_3$, N% = 7.78; found, N% = 7.7.

EXAMPLE 5

Proceeding as in Example 1(A), *N* - (4-methoxyphenyl) - 4 - trifluoromethyl - *ortho*-phenylenediamine (42 g.) is heated with 4-methoxybenzaldehyde (20 g.) in ethanol (150 ml.) and *N* - (4 - methoxyphenyl) - *N'* - (4-methoxybenzylidene) - 4 - trifluoromethyl - *ortho* - phenylenediamine (60 g.) is obtained as an oil which is utilised without purification for the next step.

The aforesaid oil (60 g.) is heated in nitrobenzene (60 ml.) as described in Example 1(B), and 5 - trifluoromethyl - 1,2 - bis - (4-methoxyphenyl) - benzimidazole (16 g., 27% yield) is obtained, m.p. 163°C. after recrystallisation from ethyl acetate. Analysis: calculated for $C_{22}H_{17}N_2O_2F_3$, N% = 7.03; found, N% = 6.9.

EXAMPLE 6

Proceeding as in Example 1(A), *N*-(4-chlorophenyl) - *ortho* - phenylenediamine (13 g.) is heated with 4 - methoxybenzaldehyde (8 g.) in ethanol (50 ml.) and *N* - (4 - chlorophenyl)-*N'* - 4 - (methoxybenzylidene)-*ortho*-phenylenediamine (25 g.) is obtained as an oil which after concentration on a water bath, is utilised as such, for the following step. The aforesaid oil (25 g.) is heated in nitrobenzene (25 ml.) as described in Example 1(B) and 1 - (4-chlorophenyl) - 2 - (4 - methoxyphenyl) benzimidazole (7 g., 35% yield) is obtained, m.p. 187° C. after recrystallisation from methanol. Analysis: calculated for $C_{20}H_{15}N_2OCl$, N% = 8.37, Cl% = 10.6; found N% = 8.23, inorganic Cl% = 11.2.

EXAMPLE 7

Proceeding as in Example 1(A), *N* - (4-chlorophenyl) - 4 - methyl - *ortho* - phenylenediamine (9 g.) is heated with 4 - methoxybenzaldehyde (5.g.) in ethanol (40 ml.), and *N* - (4 - chlorophenyl) - *N'* - (4 - methoxybenzylidene) - 4 - methyl - *ortho* - phenylenediamine is obtained as an oil which is used as such for the following step after concentration on a water bath.

Nitrobenzene (15 ml.) is added to the oil obtained as previously described in a round-bottom flask and the mixture is heated for 20 minutes under reflux. After cooling and recrystallisation of the residue from isopropanol, 5 - methyl - 1 - (4 - chlorophenyl) - 2 - (4-methoxyphenyl)benzimidazole (5 g. 42% yield) is obtained, m.p. 193°C. Analysis: calculated for $C_{21}H_{17}N_2OCl$ N% = 8.03; found, N% = 7.85.

EXAMPLE 8

Proceeding as in Example 1(A), *N* - (4-methoxyphenyl) - 4 - chloro - *ortho*-phenylenediamine (10 g.) is heated with 4 - methoxybenzaldehyde (5.5 g.) in ethanol (50 ml.) and *N* - (4 - methoxyphenyl) - *N'* - (4-methoxybenzylidene) - 4 - chloro - *ortho*-phenylene - diamine is obtained as an oil which after concentration on a water bath is utilised as such for the following step.

Nitrobenzene (20 ml.) is added to the aforesaid oil and the mixture is heated under reflux for 20 minutes. 5 - Chloro - 1,2 - bis(4-methoxyphenyl)benzimidazole (8 g., 57% yield) is obtained, m.p. 147—148°C. after recrystallisation from isopropanol. Analysis: calculated for $C_{21}H_{17}N_2O_2Cl$, N% = 7.68, Cl% = 9.73; found, N% = 7.63, Cl% = 9.17.

EXAMPLE 9

Proceeding as described in Example 7, *N*-(4 - methylphenyl) - *ortho* - phenylenediamine (12 g.) is heated with 4 - methoxybenzaldehyde (8 g.) in ethanol (40 ml.) and *N* - (4 - methylphenyl) - N - (4 - methoxybenzylidene) - *ortho* - phenylenediamine is obtained as an oil which after concentration on a water bath is utilised as such for the next step.

Nitrobenzene (18 ml.) is added to the oil thus obtained and the mixture is heated under reflux for 30 minutes. 1 - (4 - Methylphenyl)-2 - (4 - methoxyphenyl)benzimidazole (14 g., 77.7% yield) is obtained as crystals, m.p. 136° C. after recrystallisation from isopropanol. Analysis: calculated for $C_{21}H_{18}N_2O$, N% = 8.91; found, N% = 9.0.

EXAMPLE 10

Proceeding as in Example 7, *N* - (3 - trifluoromethylphenyl) - *ortho* - phenylenediamine (23 g.) is heated with 4 - methoxybenzaldehyde (13 g.) in ethanol (80 ml.) and *N*-(3 - trifluoromethylphenyl) - *N'* - (4 - methoxybenzylidene) - *ortho* - phenylenediamine is obtained as an oil which is utilised as such for the next step after concentration on a water bath.

Nitrobenzene (30 ml.) is added to the oil and the mixture is heated under reflux for 30 minutes. 1 - (3 - trifluoromethylphenyl) - 2-(4 - methoxyphenyl)benzimidazole (9 g., 30% yield) is obtained as crystals, m.p. 144°C. after recrystallisation from ethanol. Analysis: : calculated for $C_{21}H_{15}N_2OF_3$, N% = 7.61; found, N% = 7.53.

EXAMPLE 11

6.5 g. of *N* - (3 - chlorophenyl) - 1,2-phenylenediamine, 4 g. of 4 - methoxybenzaldehyde, and 30 ml. of absolute ethanol are introduced into a 100 ml. round-bottomed flask equipped with a condenser. Heating takes place under reflux for one hour. The alcohol is evaporated *in vacuo* and *N* - (3 - chlorophenyl) - N' - (4 - methoxybenzylidene)-

ortho - phenylenediamine is obtained as an oil, which is used as such for the following stage.

10 ml. of nitrobenzene are added to the oil and the mixture is heated under reflux for 20 minutes, and allowed to cool. The crystals are separated, washed with petroleum ether, and recrystallised from ethanol. 5 g. (50% yield) of 1 - (3 - chlorophenyl) - 2 - (4 - methoxyphenyl)benzimidazole, m.p. 192°C., are obtained. The analysis of this compound, of which the empirical formula is $C_{20}H_{15}N_2OCl$, gave the following results:

	N	Cl
Calculated: %	8.37	10.61
Found: %	8.27	9.65

EXAMPLE 12

Following the procedure described in Example 11, but starting with 21 g. of *N* - (4-methoxyphenyl) - 1,2 - phenylenediamine, 14 g. of 4 - chlorobenzaldehyde and 80 ml. of absolute ethanol, *N* - (4' - methoxyphenyl)-*N'* - (4 - chlorobenzylidene) - 1,2 - phenylenediamine is obtained as an oil, which is used as such after concentration for the following stage.

27 ml. of nitrobenzene are added to the oil and the mixture is heated under reflux for 20 minutes, and then allowed to cool. The crystals formed are separated and washed with petroleum ether. 25 g. (79% yield) of 1 - (4-methoxyphenyl) - 2 - (4 - chlorophenyl)-benzimidazole, recrystallised from isopropanol and melting at 158°C., are obtained. The analysis of this product, of which the empirical formula is $C_{20}H_{15}N_2OCl$, gave the following results:

	N	Cl
Calculated: %	8.37	10.61
Found: %	8.34	10.65

EXAMPLE 13

Following the procedure described in Example 11, but startitng with 10 g. of *N* - (4-methoxyphenyl) - 1,2 - phenylenediamine, 11 g. of 4 - (2 - diethylaminoethoxy)benzaldehyde and 40 ml. of absolute ethanol, *N* - (4-methoxyphenyl) - *N'* - [4 - (2 - diethylaminoethoxy) - benzylidene] - 1,2 - phenylenediamine is obtained as an oil which is used as such for the following stage.

12 ml. of nitrobenzene are added to the oil and the mixture is heated under reflux for 20 minutes. After steam distillation of the excess nitrobenzene, the residue is treated with boiling cyclohexane. After filtration and cooling, the crystals formed are separated. 8 g (43% yield) of 1 - (4 - methoxyphenyl) - 2 - [4-(2 - diethylaminoethoxy) - phenyl]benzimidazole, recrystallised from isopropanol and melting at 110°C., are obtained. The analysis of this product, of which the empirical formula is $C_{26}H_{29}N_3O_2$, gave the following results:

Amino nitrogen: %, calculated 6.74, found, 6.68;

Total nitrogen, %, calculated 10.12, found 10.0.

EXAMPLE 14

Following the procedure described in Example 11, but starting with 8.5 g. of *N* - (4-methoxyphenyl) - 4 - trifluoromethyl - 1,2-phenylenediamine, 4.5 g. of 4 - hydroxybenzaldehyde and 30 ml. of absolute ethanol, *N*-(4 - methoxyphenyl) - *N'* - (4 - hydroxybenzylidene) - 4 - trifluoromethyl - 1,2 - phenylenediamine is obtained as an oil which is used as such for the following stage, after concentration on a water bath.

15 ml. of nitrobenzene are added to the oil and, after heating under reflux for 20 minutes and cooling, 1.2 g. (10% yield) of (5 - trifluoromethyl) - 1 - (4 - methoxyphenyl) - 2-(4 - hydroxyphenyl) - benzimidazole, recrystallised from isopropanol and melting at 256° C., are obtained. The analysis of this product, of which the empirical formula is

$$C_{21}H_{15}N_2O_2F_3$$

gave the following results:

Total nitrogen: %, calculated 7.29;
found 7.13

EXAMPLE 15

Following the procedure described in Example 11, but starting with 20 g. of *N* - (2-chlorophenyl) - 1,2 - phenylenediamine, 12 g. of 4 - methoxybenzaldehyde and 80 ml. of absolute ethanol, *N* - (2 - chlorophenyl) - *N'*-(4 - methoxybenzylidene) - 1,2 - phenylenediamine is obtained as an oil which is used as such for the following stage after concentration.

28 ml. of nitrobenzene are added to the oil and the mixture is heated under reflux for 20 minutes. After cooling, the crystals formed are separated and washed with petroleum ether. 14 g. (47% yield) of 1 - (2 - chlorophenyl)-2 - (4 - methoxyphenyl)benzimidazole, recrystallised from isopropanol and melting at 159° C., are obtained. The analysis of this product, of which the empirical formula is

$$C_{20}H_{15}N_2OCl,$$

gave the following results:

	N	Cl
Calculated: %	8.37	10.61;
found: %	8.31	10.82

EXAMPLE 16

Following the procedure described in Example 11, but starting with 19 g. of *N* - (4-methoxyphenyl) - 5 - methyl - 1,2 - phenylenediamine, 11 g. of 4 - methoxybenzaldehyde

and 80 ml. of absolute ethanol, *N* - (4-methoxyphenyl) - *N'* - (4 - methoxybenzylidene)-5 - methyl - 1,2 - phenylenediamine is obtained as an oil which is used as such for the following stage, after concentration on a water bath.

30 ml. of nitrobenzene are added to the oil and, after heating under reflux for 20 minutes, the excess nitrobenzene is removed by steam distillation. The crystals formed are separated and washed, and then heated in 20 ml. of 10% hydrochloric acid. After cooling and separation, 14 g. of 6 - methyl - bis - 1,2 - (4-methoxyphenyl)benzimidazole hydrochloride, recrystallised from isopropanol and melting at 192 to 193°C. with decomposition, are obtained. The analysis of this product, of which the empirical formula is (in the case of the base) $C_{22}H_{20}N_2O_2$, gave the following results:

	N	Cl
Calculated: %	7.36	9.33;
found: %	7.28	9.31.

EXAMPLE 17

Following the procedure described in Example 11, but starting with 8.4 g. of *N* - (4-methoxyphenyl) - 1,2 - phenylenediamine, 5.6 g. of 2 - chlorobenzaldehyde and 30 ml. of absolute ethanol, *N* - (4 - methoxyphenyl)-*N'* - (2 - chlorobenzylidene) - 1,2 - phenylenediamine is obtained as an oil which is used as such for following stage, after concentration on a water bath.

15 ml. of nitrobenzene are added to this oil and the mixture is heated for 20 minutes on a water bath. The excess nitrobenzene is removed by steam distillation. The crystals formed are recrystallised from isopropanol and separated. They are heated with 10% hydrochloric acid, separated and washed with water. 3.5 g. (26% yield of 1 - (4 - methoxyphenyl)-2 - (2 - chlorophenyl)benzimidazole hydrochloride, recrystallised from ethanol and melting at 200°C. with decomposition, are obtained. The analysis of this product, of which the empirical formula is (in the case of the base) $C_{20}H_{15}N_2OCl$, gave the following result:

Total nitrogen: %, calculated 7.55;
found 7.44.

EXAMPLE 18

Following the procedure described in Example 11, but starting with 8.4 g. of *N* - (4-methoxyphenyl) - 1,2 - phenylenediamine, 5.6 g. of 3 - chlorobenzaldehyde and 30 ml. of absolute ethanol, *N* - (4 - methoxyphenyl) - *N'* - (3 - chlorobenzylidino) - 1,2 - phenylenediamine is obtained as an oil which is used as such for the following stage after concentration.

12 ml. of nitrobenzene are added to the oil and the mixture is refluxed for 20 minutes. The excess nitrobenzene is removed by steam distillation and 7.3 g. (54% yield) of 1 - (4-methoxyphenyl) - 2 - (3 - chlorophenyl)benzimidazole, recrystallised from a mixture of isopropanol and petroleum ether, m.p. 122°C., are obtained. The analysis of this product, of which the empirical formula is $C_{20}H_{15}N_2OCl$, gave the following result:

Amino nitrogen: %, calculated 4.18;
found 4.18.

EXAMPLE 19

Following the procedure described in Example 11, but starting with 14 g. of *N* - (4-methoxyphenyl) - 1,2 - phenylenediamine, 9 g. of 2 - methoxybenzaldehyde and 50 ml. of absolute ethanol, *N* - (4 - methoxyphenyl)-*N'* - (2 - methoxybenzylidene)-1,2-phenylenediamine is obtained as an oil which is used as such for the following stage, after concentration on a water bath.

25 ml. of nitrobenzene are then added to the oil and the mixture is heated under reflux for 20 minutes. The excess nitrobenzene is removed and 7 g (35% yield) of 1 - (4-methoxyphenyl) - 2 - (2 - methoxyphenyl)benzimidazole, recrystallised from a mixture of isopropanol and petroleum ether, m.p. 124° C., are obtained. The analysis of this product, of which the empirical formula is $C_{21}H_{18}N_2O_2$, gave the following result:

Acidity: 100.1% of theory.

EXAMPLE 20

Following the procedure described in Example 11, but starting with 10.6 g. of *N* - (4-methylphenyl) - 4 - methyl - 1,2 - phenylenediamine, 6 g. of 4 - methylbenzaldehyde and 60 ml. of absolute ethanol, *N* - (4 - methylphenyl) *N'* - (4 - methylbenzylidene) - 4-methyl - 1,2 - phenylenediamine is obtained as an oil which is used as such for the following stage, after concentration on a water bath.

18 ml. of nitrobenzene are added and the mixture is heated under reflux for 20 minutes. After cooling, the crystals which have formed are separated and washed. 9 g. (60% yield) of 5 - methyl - 1,2 - bis - (4 - methylphenyl)-benzimidazole, recrystallised from isopropanol, m.p. 142°C., are obtained. The analysis of this product, of which the empirical formula is $C_{22}H_{20}N_2$, gave the following result:

Amino nitrogen: % calculated 4.49;
found 4.52.

EXAMPLE 21

Following the procedure described in Example 11, but starting with 9 g. of *N* - (4-methoxyphenyl) - 1,2 - phenylenediamine, 5 g. of 4 - methylbenzaldehyde and 30 ml. of absolute ethanol, *N* - (4 - methoxyphenyl) - *N'*-(4 - methylbenzylidene) - 1,2 - phenylenediamine is obtained as an oil which is used as such for the following stage, after concentration on a water bath.

18 ml. of nitrobenzene are added and the mixture is heated under reflux for 20 minutes. After cooling, the crystals formed are separ-

ated and washed. 5.3 g. (43% yield) of 1-(4-methoxyphenyl) - 2 - (4 - methylphenyl)benzimidazole, recrystallised from ethyl acetate, m.p. 149°C., are obtained. The analysis of this product, of which the empirical formula is $C_{21}H_{18}N_2O$, gave the following result:

Amino nitrogen: % calculated 4.46; found 4.64.

EXAMPLE 22

Following the procedure described in Example 11, and starting with 2.14 g. of *N* - (4-methoxyphenyl) - 1,2 - phenylenediamine, 1.56 g. of 4 - carboxybenzaldehyde and 20 ml. of absolute ethanol, 3.5 g. of *N* - (4 - methoxyphenyl) - *N'* - (4 - carboxybenzylidene) - 1,2-phenylenediamine are obtained as orange-coloured crystals, m.p. about 210°C.

These crystals are dissolved in 7 ml. of nitrobenzene and the mixture is refluxed for 15 minutes. The mixture is allowed to cool and the crystals formed are separated and washed. 2 g. (60% yield) of 1 - (4 - methoxyphenyl) - 2 - (4 - carboxyphenyl)benzimidazole, recrystallised from ethyl acetate, m.p. 268°C., are obtained. The analysis of this product, of which the formula is $C_{21}H_{16}N_2O_3$, gave the following results:

Amino nitrogen: % calculated 4.09
found 3.96
Acidity: 100.3% of theory

The pharmacological properties of the benzimidazoles of Formula I have been studied.

Toxicity

When administered orally to mice in a dose of 5 g. per kg. 1,2 - bis - (4 - methoxyphenyl)-benzimidazole (Compound A) caused no deaths nor toxic symptoms in the experimental animals. Two other compounds of Formula I, namely 6 - methyl - 1,2 - bis - 4 - methoxyphenyl - benzimidazole (Compound B) and 5-trifluoromethyl - 1,2 - bis - 4 - methoxyphenyl - benzimidazole (Compound C), caused no mortality in mice when administered orally in a dose of 3 g. per kg.

Pharmacodynamic Activity

Anti-inflammatory Activity

The compounds of Formula I have been tested for anti-inflammatory activity by the following tests: oedema of the rats paw induced by carraghenin (Proc. Soc. Exp. Biol. Med., 1962, *3*, 544); air pouch granuloma caused by croton oil in the rat (Robert *et al.* Acta Endocrinol., *25*, 105, 1957); and micro-abscess caused by terebenthine in the rat (Arch. Intern. Pharmacodyn. *137*, 199, 1962). The following results were obtained:

Carraghenin oedema

Time in hours after administration of carraghenin	Percentage Activity of compound A		Percentage Activity of compound C	
	15 mg./kg. *per os*	30 mg./kg. *per os*	15 mg./kg. *per os*	90 mg./kg. *per os*
2	20.6	30.4	20	45.3
3	26.9	32.1	22.8	46.5
4	20.6	29.6	21.3	50.4
5	20.6	29.7	19.4	54.6
6	—	14.4	11.4	62.8

Croton oil granuloma

Compound A in a dose of 15 mg. per kg. adminstered orally shows a 45.6% activity in reducing the volume of exudate. Compound B, in a dose of 30 mg./kg., shows an activity of 38.8% in reducing the volume of exudate. The compound A when administered in a dose of 90 mg./kg. orally shows, in three cases out of five, reduction in collagen, in the fibroblastic reaction, and in acid mucopolysaccharides.

Micro-abscess caused by terebenthine.

When administered orally in the rat a dose of 16 mg./kg., compound A shows in all six cases studied a strong reduction of collagen and a disappearance of acid gluco polysaccharides.

These results show that the compounds of Formula I have a distinct anti-inflammatory activity.

Analgesic Activity

The analgesic activity of compound A was compared with that of amidopyrine using the heated plate test with mice (see J. Pharmacol, Exp. Therap., 1944, *80*, 300). The results obtained are shown in the following table:

Dose	% analgesia after (hours)			
	1	2	3	4
50 mg./kg. *per os*				
amidopyrine	24.2 (12)	11.5 (12)	10 (6)	2.5 (6)
compound A	7.6	34	33.5	13.5
100 mg./kg. *per os*				
amidopyrine	36 (6)	32 (6)	11 (6)	29 (6)
compound A	33.5 (6)	18 (6)	22 (6)	17 (6)

()=number of test animals for each dosage

These results show that aminopyrine has a very rapid action which, however, diminishes after the second hour while compound A has a prolonged action which is still strong four hours after administration.

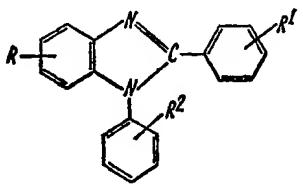
The pharmacodynamic properties of the compound of Formula I render the latter useful in the treatment of maladies such as inflammatory rheumatism, rheumatoid polyarthritis, ankylosing spondylarthritis, degenerative rheumatism, coxitis, abarticular affections, periarthritis, rachialgia, and radiculalgia.

The present invention accordingly includes within its scope pharmaceutical compositions comprising one or more of the compounds of formula I or acid addition salts thereof, in association with a solid or liquid pharmaceutical carrier and suitable for administration in man, for example by the oral, parenteral or rectal route. Such compositions may be in the form of simple tablets, tablets having a gastric or enteric coating, capsules, gellules, suppositories, ointments, and drinkable or injectable solutions or suspensions. These different compositions may be made using excipients which are commonly used in the art suitable for the pharmaceutical form chosen; e.g. starch, talc, magnesium stearate, lactose, resins, semi-synthetic glycerides, natural or synthetic excipients for ointments, aqueous or oil vehicles, emulsifiers, adjuvants, preservatives and various flavouring agents.

The dose administered depends on the patient and the seriousness of the affection being treated. In general, the oral dose administered daily in man will be from 0.1 to 5 g.

WHAT WE CLAIM IS:—

1. Benzimidazoles of the formula:



in which R represents hydrogen, halogen, trifluoromethyl, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms, and R^1 and R^2 are the same or different and are each halogen, trifluoromethyl, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, hydroxy, aminoalkoxy of 1 to 4 carbon atoms, alkylaminoalkoxy of 1 to 4 carbon atoms in each alkyl residue, dialkylaminoalkoxy of 1 to 4 carbon atoms in each alkyl residue, or carboxy, and their acid addition salts.

2. Benzimidazoles as claimed in claim 1 in which R represents hydrogen, halogen, trifluoromethyl, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms, and R^1 and R^2 are the same or different and are each halogen, trifluoromethyl, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms, and their acid addition salts.

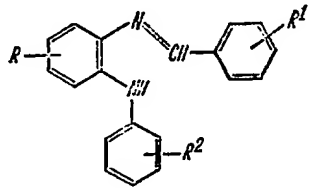
3. 1,2 - Bis(4 - methoxyphenyl)benzimidazole and its acid addition salts.

4. 6 - Methyl - 1,2 - bis(4 - methoxyphenyl)-benzimidazole and its acid addition salts.

5. 5 - Trifluoromethyl - 1,2 - bis - (4-methoxyphenyl)benzimidazole and its acid addition salts.

6. Any one of the benzimidazoles claimed in claim 1 described in the foregoing Examples, and their acid addition salts.

7. Process for the preparation of a benzimidazole as claimed in claim 1 which comprises oxidizing a compound of the formula:



in which R, R^1, and R^2 are as defined in claim 1.

8. Process according to claim 7 in which R, R^1, and R^2 are as defined in claim 2.

9. Process according to claim 7 or 8 in which the oxidation is effected by heating with nitrobenzene or *meta*-dinitrobenzene.

10. Process according to claim 7 or 8 substantially as described in the Examples.

11. A benzimidazole as claimed in claim 1 or 2 or an acid addition salt thereof when prepared by the process claimed in any of claims 7 to 10.

12. A pharmaceutical composition comprising one or more benzimidazoles as claimed in any one of claims 1 to 6 and 11 or a non-toxic acid addition salt thereof, in association with a solid or liquid pharmaceutical carrier.

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